Economic Burden among Commercially Insured Patients with Systemic Sclerosis in the United States

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ABSTRACT. Objective. To quantify healthcare resource utilization (HRU), work loss, and annual direct and indirect healthcare costs among patients with systemic sclerosis (SSc) compared to matched controls in the United States.

Methods. Data were obtained from a large US commercial claims database. Patients were ≥ 18 years old at the index date (first SSc diagnosis) and had ≥ 1 SSc diagnosis in the inpatient (IP) or emergency room (ER) setting, or ≥ 2 SSc diagnoses on 2 different dates in the outpatient (OP) setting between January 1, 2005, and March 31, 2015; continuous enrollment was required during the followup period (12 months after the index date). Individuals with no SSc diagnoses were matched 1:1 to patients with SSc. Wilcoxon signed-rank and McNemar tests were used for comparisons and regressions with generalized estimating equations for adjusted OR (aOR) and incidence rate ratios (IRR) between 2 cohorts.

Results. There were 2192 pairs of patients with SSc and matched controls included (mean age 57.6 yrs; 84.3% female); of these, 233 were eligible for work loss/indirect cost analyses. Compared to matched controls, patients with SSc had significantly higher HRU and costs during the 1-year followup period, IP admissions (adjusted IRR = 2.4), IP hospitalization days (adjusted IRR = 3.1), ER visits (adjusted IRR = 2.0), OP visits (adjusted IRR = 2.3), and days of work loss (adjusted IRR = 2.6). The adjusted difference in annual direct and indirect costs was US\$12,820 and \$3103, respectively (all $p < 0.0001$).

Conclusion. Patients with SSc had a high direct and indirect economic burden postdiagnosis. (First Release February 15 2019; J Rheumatol 2019;46:920–7; doi:10.3899/jrheum.180445)

Key Indexing Terms:

SYSTEMIC SCLEROSIS

DIRECT HEALTHCARE COSTS

HEALTHCARE RESOURCE UTILIZATION

WORK PRODUCTIVITY LOSS

INDIRECT COSTS

Scleroderma or systemic sclerosis (SSc) is a chronic autoimmune disease of the connective tissue characterized by fibroproliferative vasculopathy and progressive fibrosis of the skin and internal organs¹. The prevalence of SSc is estimated to range from 50 to 300 per million across the world, with one of the highest prevalence rates observed in

the United States at 240 per million^{2,3}. Cumulative survival rates of 5 and 10 years for patients with SSc were estimated at 74.9% and 62.5%, respectively⁴; lung involvement was the most common cause of death among patients with SSc-related deaths⁴.

Because of its clinical heterogeneity, SSc is a challenging disease to manage^{5,6}. Currently, there are no disease-modifying therapies approved by the US Food and Drug Administration and treatment mostly depends on the type and severity of organ involvement^{5,6,7}. Despite limited evidence supporting their effectiveness, nonselective immunosuppressive treatments are commonly used^{6,8}. Hematopoietic stem cell transplantation has been shown to be effective in select patients with more severe skin thickening^{9,10,11}. Biologic agents may be administered in refractory cases, though the evidence in support of such an approach is limited^{6,8}.

Given the considerable comorbidity burden of SSc and the availability of limited, and only partly effective, treatment options, it is not surprising that substantial healthcare costs associated with SSc have been reported¹². However, the economic burden of SSc has been estimated in a limited number of studies^{12–17}, with only 2 such studies^{18,19} including

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This study was funded by Boehringer Ingelheim Pharmaceuticals Inc.

Y. Fan is a salaried employee of Boehringer Ingelheim Pharmaceuticals Inc. Z. Zhou, W. Tang, X. Liu, D. Thomason, Z.Y. Zhou, and D. Macaulay are employees of Analysis Group Inc., which has received consultancy fees from Boehringer Ingelheim Pharmaceuticals Inc.

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Accepted for publication October 16, 2018.

US patients. One of them (Furst, *et al*¹⁸) found that patients with SSc had significantly higher annual healthcare costs and healthcare resource utilization (HRU) than matched controls but only included data up to 2008, and thus may be outdated and not reflective of the current treatment landscape. More recently, Fischer, *et al*¹⁹ also found high annual healthcare costs among patients with SSc in the United States but did not compare them with those of controls and did not include HRU or indirect costs. Moreover, neither of these US studies assessed work productivity loss among patients with SSc.

Therefore, to provide a more comprehensive and current estimate of the burden of illness of SSc, this study quantified annual HRU, work loss, and direct and indirect costs (i.e., costs associated with work productivity loss due to disability or medically related absenteeism) among patients with SSc compared to individuals without SSc in US clinical practice.

MATERIALS AND METHODS

Data source. Data for this study were obtained from the OptumHealth Care Solutions Inc. database covering 84 self-insured Fortune 500 companies, including medical and pharmaceutical claims for over 19 million privately insured individuals and their families. The database covers a range of industries, job classifications, and locations across the United States. Work productivity loss data (i.e., claims associated with short- and long-term disability or medically related absenteeism) are available for the employees of 44 out of the 84 companies in the database. All the data used in this study were de-identified and fully compliant with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act. No ethical review by an institutional review board was required. Data from Q3 2004 to Q1 2016 were used.

Patients with SSc. Patients with SSc were eligible for inclusion if they had at least 1 medical claim with a diagnosis of SSc (International Classification of Diseases, 9th Revision, Clinical Modification code 710.1) in the inpatient (IP) or emergency room (ER) setting, or at least 2 medical claims with diagnoses of SSc on 2 different dates in the outpatient (OP) or other settings between January 1, 2005, and March 31, 2015. Two medical claims were required to limit potential misclassification, which tends to be higher in the OP setting compared to the IP and ER settings, as commonly done in the literature^{18,19}. The date of the first observed SSc diagnosis was defined as the index date. Patients were further required to be at least 18 years of age at the index date, have continuous enrollment in their healthcare plan for 6 months prior to the index date (baseline period) and 12 months following the index date (followup period), and have no claims with a diagnosis of SSc during the baseline period.

To be eligible for work loss and indirect cost analyses, patients were additionally required to be primary policyholders (this is because the database contains salary information only for primary policyholders), actively employed on the index date, and continuously employed during the 12-month followup period with available work loss data.

Matched controls. Controls were required to have no diagnosis of SSc in their entire claims history. For the controls, the index date was selected as the same calendar date as that of the patients with SSc to whom they were matched. Controls were matched exactly with a 1:1 ratio to patients with SSc on age at the index date (measured in years), sex, region of residence (i.e., Northwest, Midwest, South, West, unknown), and insurance type (i.e., preferred provider organization, point of service, indemnity, unknown/other). Specifically, to be matched to a patient, a control was required to have the exact same value for each and every characteristic of the patient. If there were multiple potential controls who matched a certain patient exactly, the control was randomly selected from the pool of potential matches; those who were not matched to that particular patient were returned to the pool of potential matches for the next round of matching. The controls were further

required to have continuous enrollment in their healthcare plan during the baseline and followup periods.

Baseline characteristics. Baseline characteristics included demographics (e.g., age, sex), the index year (defined as the year of the index date), a modified Charlson comorbidity index (CCI)²⁰ that excluded SSc diagnoses, individual CCI components, and other SSc-related comorbidities. All-cause HRU and healthcare costs (i.e., medical and pharmacy costs) were also measured during the baseline period.

HRU and clinical outcomes in the followup period. During the followup period, HRU measures included IP admissions and total IP hospitalization days, ER visits, OP visits, specialist visits, and other visits (including laboratory tests and medical services at home). In addition, selected procedures, medication use, and SSc-related comorbidities, as well as the modified CCI, were also measured.

Direct healthcare costs in the followup period. Annual direct healthcare costs measured during the followup period included medical costs and pharmacy costs and were calculated for both patients with SSc and matched controls. Total medical costs included IP costs, ER costs, OP costs, and costs for other visits (including laboratory tests and medical services at home, etc.). All costs were inflated to 2016 US dollars (US\$).

Work loss in the followup period. Work loss analyses were conducted among individuals with available work loss data. Work loss during the followup period included total days of work loss due to disability and days of medically related absenteeism. These were identified based on the use of medical services (e.g., an office or hospital inpatient visit) during business days (Monday through Friday) as well as the gap days between the injury date (i.e., the date of the injury that resulted in the disability claim; obtained from medical claims) and the start date of disability (obtained from disability claims). It was assumed that each hospitalization day or emergency department visit accounted for a full day of work loss, while each outpatient or other visit accounted for half a day of work loss.

Indirect costs in the followup period. Annual indirect costs were calculated among the subset of patients with available work loss data. Indirect costs during the followup period included medically related absenteeism costs and disability costs. Medically related absenteeism costs were calculated based on individual employees' income information obtained from eligibility files and days of medically related absenteeism, defined above. Annual disability costs were calculated based on individual employees' income information obtained from eligibility files and days of disability, which were identified based on the dates of disability provided in disability claims. All indirect costs were inflated to 2016 US\$.

Statistical analysis. For baseline characteristics and clinical outcomes during the followup period, mean and SD were reported for continuous variables; frequency and percentage were reported for categorical variables. Descriptive comparisons were made between patients with SSc and matched controls using Wilcoxon signed-rank tests for continuous variables and McNemar tests for categorical variables.

For HRU and work loss during the followup period, the proportions of patients with any event and mean counts of events were described and compared between patients with SSc. In addition, aOR and incidence rate ratios (IRR) between patients with SSc and matched controls were calculated using multivariable regressions with generalized estimating equations and with binomial distributions for OR and Poisson distributions accounting for overdispersion for IRR. To improve the precision of the coefficient estimates, the regressions controlled for baseline covariates, including age, sex, index year (i.e., 2005–2010 vs 2011–2015), region of residence (i.e., South vs other), insurance type (i.e., preferred provider organization vs other), industry category (i.e., manufacturing, transportation, government vs other), and selected baseline comorbidities that were not related to SSc and with prevalence > 5% in any cohort (i.e., diabetes without chronic complication, any malignancy including leukemia and lymphoma).

For annual direct healthcare and indirect costs, descriptive costs for the followup period were compared between patients with SSc and matched controls. In multivariable analyses, differences in mean adjusted costs

between patients with SSc and matched controls were estimated using multi-variable regression with generalized estimating equations and with the Tweedie distribution, controlling for the same covariates as those used in the HRU and work loss analyses.

RESULTS

Baseline period. A total of 2192 patients with SSc and 2192 matched controls were included in the study; of these, 233 pairs were eligible for inclusion in the work loss and indirect cost analyses (Figure 1).

Baseline characteristics are presented in Table 1. For both patients with SSc and matched controls, mean age at the index date was 57.6 years and the proportion of females was 84.3%. The modified CCI score, which excluded SSc, was significantly higher for patients with SSc than for matched controls (0.7 vs. 0.3, $p < 0.0001$; Table 1). Rheumatic disease (excluding SSc) and chronic pulmonary disease were the 2 most common comorbidities for patients with SSc and were significantly more prevalent among patients with SSc than matched controls (rheumatic disease: 21.0% vs 1.6%, $p < 0.0001$; chronic pulmonary disease: 14.5% vs 5.8%, $p < 0.0001$; Table 1).

All-cause HRU measures at baseline were significantly higher for patients with SSc than matched controls (all $p < 0.0001$; Table 1). Similarly, all-cause costs at baseline were also significantly higher for patients with SSc than for matched

controls (all $p < 0.0001$; Table 1). Specifically, baseline total costs were \$9382 for patients with SSc and \$3058 for matched controls ($p < 0.0001$), with medical costs accounting for \$7363 for patients with SSc and \$2121 for matched controls.

HRU and clinical outcomes in the followup period. Unadjusted measures of clinical outcomes and rates of medication use were generally higher among patients with SSc than matched controls (Table 2). Unadjusted and adjusted HRU measures were all significantly higher among patients with SSc than among matched controls (Table 2 and Table 3). In particular, patients with SSc versus matched controls had more IP admissions (0.7 vs 0.3 events; adjusted IRR 2.4, 95% CI 2.2–2.6), days of IP hospitalization (3.7 vs 1.1 days; adjusted IRR 3.1, 95% CI 2.9–3.4), ER visits (0.7 vs 0.3 events; adjusted IRR 2.0, 95% CI 1.9–2.2), OP visits (23.8 vs 10.3 events; adjusted IRR 2.3, 95% CI 2.2–2.4), and other visits (3.0 vs 1.0 events; adjusted IRR 2.9, 95% CI 2.7–3.1; all $p < 0.0001$). Further, the odds of any IP admission (aOR 3.8, 95% CI 3.2–4.5), ER visit (aOR 1.9, 95% CI 1.7–2.1), and any other visit (aOR 2.2, 95% CI 2.0–2.6) were higher among patients with SSc than among matched controls (all $p < 0.0001$; Table 3).

Direct healthcare costs in the followup period. Unadjusted total annual direct healthcare costs during the followup period were significantly higher for patients with SSc (\$22,016, of

Figure 1. Sample selection. ¹Index date was defined as the date of the first SSc diagnosis between January 1, 2005, and March 31, 2015. ²The baseline period was defined as the 6-month period before the index date. ³The followup period was defined as the 12-month period following the index date. ⁴Patients were eligible for work loss analyses if they were primary policyholders, actively employed at the index date, and continuously employed during the followup period. SSc: systemic sclerosis.

Table 1. Baseline characteristics.

Characteristics	Patients with SSc, n = 2192		Matched Controls, n = 2192		p
Demographics					
Age at the index date, ¹ yrs, mean (SD)	57.6	(13.8)	57.6	(13.8)	
Female, ¹ n (%)	1847	(84.3)	1847	(84.3)	
Region of residence at the index date, ¹ n (%)					
South	702	(32.0)	702	(32.0)	
Midwest	551	(25.1)	551	(25.1)	
Northeast	542	(24.7)	542	(24.7)	
West	269	(12.3)	269	(12.3)	
Unknown	128	(5.8)	128	(5.8)	
Insurance plan at the index date, ¹ n (%)					
Preferred provider organization	1154	(52.6)	1154	(52.6)	
Indemnity	656	(29.9)	656	(29.9)	
Point of service	313	(14.3)	313	(14.3)	
Other/unknown	69	(3.1)	69	(3.1)	
Employment industry, n (%)					
Manufacturing	522	(23.8)	480	(21.9)	0.0650
Transportation	381	(17.4)	391	(17.8)	0.6381
Government/religion/education services	247	(11.3)	243	(11.1)	0.7440
Other	1042	(47.5)	1078	(49.2)	0.1785
Index year, ¹ n (%)					
2005–2010	1514	(69.1)	1514	(69.1)	
2011–2015	678	(30.9)	678	(30.9)	
SSc-related comorbidities, n (%)					
Systemic lupus erythematosus	251	(11.5)	3	(0.1)	< 0.0001
Gastroesophageal reflux disease	246	(11.2)	80	(3.6)	< 0.0001
Rheumatoid arthritis	212	(9.7)	22	(1.0)	< 0.0001
Depression	177	(8.1)	133	(6.1)	0.0095
Peripheral vascular disease	116	(5.3)	43	(2.0)	< 0.0001
Atherosclerosis	57	(2.6)	17	(0.8)	< 0.0001
Sjögren syndrome	82	(3.7)	5	(0.2)	< 0.0001
Chronic liver disease	36	(1.6)	8	(0.4)	< 0.0001
Pain	30	(1.4)	9	(0.4)	0.0006
Lymphoma	22	(1.0)	9	(0.4)	0.0196
Acute myocardial infarction	18	(0.8)	7	(0.3)	0.0278
Modified CCI, ² mean (SD)	0.7	(1.2)	0.3	(0.8)	< 0.0001
Components of modified CCI, n (%)					
Rheumatic disease (excluding SSc) ³	460	(21.0)	34	(1.6)	< 0.0001
Chronic pulmonary disease ⁴	318	(14.5)	127	(5.8)	< 0.0001
Diabetes without chronic complication	163	(7.4)	156	(7.1)	0.6805
Any malignancy including leukemia and lymphoma	130	(5.9)	108	(4.9)	0.1416
Peripheral vascular disease	116	(5.3)	43	(2.0)	< 0.0001
Congestive heart failure	97	(4.4)	40	(1.8)	< 0.0001
Cerebrovascular disease	89	(4.1)	39	(1.8)	< 0.0001
Renal disease	63	(2.9)	15	(0.7)	< 0.0001
Mild liver disease	59	(2.7)	18	(0.8)	< 0.0001
Diabetes with chronic complications	34	(1.6)	35	(1.6)	0.9028
Myocardial infarction	22	(1.0)	10	(0.5)	0.0339
All-cause HRU, mean (SD)					
No. IP admissions	0.3	(1.1)	0.1	(1.0)	< 0.0001
No. ER visits	0.3	(1.2)	0.2	(1.0)	< 0.0001
No. OP visits	9.8	(9.2)	5.1	(7.0)	< 0.0001
No. other visits	1.0	(2.9)	0.4	(1.7)	< 0.0001
All-cause healthcare costs ⁵ , mean (SD)					
Medical costs	7363.6	(27,931.6)	2121.1	(8210.5)	< 0.0001
Pharmacy costs	2018.4	(4873.6)	937.5	(2283.4)	< 0.0001
Total costs	9382.0	(28,894.0)	3058.6	(8693.3)	< 0.0001

¹ P value not calculated because patients with SSc and controls were matched on this characteristic. ² Excluded SSc diagnoses from the rheumatic disease component. ³ Includes giant systemic lupus erythematosus, sicca syndrome, dermatomyositis, polymyositis, rheumatoid arthritis, Felty syndrome, rheumatoid lung, and polymyalgia rheumatica. ⁴ Includes chronic airway obstruction, asbestosis, asthma, bronchiectasis, bronchitis, emphysema, extrinsic allergic alveolitis, pneumoconiosis, pulmonary heart diseases, pulmonary manifestations including secondary pulmonary hypertension, and respiratory conditions. ⁵ In 2016 US\$. SSc: systemic sclerosis; HRU: healthcare resource utilization; CCI: Charlson comorbidity index; IP: inpatient; ER: emergency room; OP: outpatient.

Table 2. Unadjusted HRU and clinical outcomes in the followup period¹.

Variables	Patients with SSc, n = 2192		Matched Controls, n = 2192		p
All-cause HRU, n (%)					
Rheumatologist visit	1176	(53.6)	56	(2.6)	< 0.0001
Cardiologist visit	895	(40.8)	297	(13.5)	< 0.0001
Pulmonologist visit	627	(28.6)	71	(3.2)	< 0.0001
Dermatologist visit	616	(28.1)	335	(15.3)	< 0.0001
Medication use, n (%)					
Oral corticosteroids	755	(34.4)	261	(11.9)	< 0.0001
Nonbiologic immunomodulators	414	(18.9)	21	(1.0)	< 0.0001
Methotrexate	227	(10.4)	16	(0.7)	< 0.0001
Mycophenolate mofetil	116	(5.3)	0	(0.0)	–
Azathioprine	83	(3.8)	3	(0.1)	< 0.0001
Cyclophosphamide	40	(1.8)	2	(0.1)	< 0.0001
Cyclosporine	2	(0.1)	0	(0.0)	–
Biologic immunomodulators	15	(0.7)	2	(0.1)	0.0016
Rituximab	14	(0.6)	0	(0.0)	–
Tocilizumab	1	(0.0)	2	(0.1)	0.5637
Tests and procedures, n (%)					
Chest radiograph	989	(45.1)	352	(16.1)	< 0.0001
Serologic test	684	(31.2)	105	(4.8)	< 0.0001
HRCT or CT	518	(23.6)	67	(3.1)	< 0.0001
Antinuclear antibody test	479	(21.9)	55	(2.5)	< 0.0001
SSc-related comorbidities, n (%)					
Gastroesophageal reflux disease	549	(25.0)	122	(5.6)	< 0.0001
Systemic lupus erythematosus	423	(19.3)	4	(0.2)	< 0.0001
Rheumatoid arthritis	302	(13.8)	33	(1.5)	< 0.0001
Depression	248	(11.3)	188	(8.6)	0.0028
Peripheral vascular disease	209	(9.5)	61	(2.8)	< 0.0001
Atherosclerosis	111	(5.1)	31	(1.4)	< 0.0001
Sjögren syndrome	176	(8.0)	6	(0.3)	< 0.0001
Pain	71	(3.2)	32	(1.5)	< 0.0001
Chronic liver disease	66	(3.0)	14	(0.6)	< 0.0001
Lymphoma	33	(1.5)	6	(0.3)	< 0.0001
Acute myocardial infarction	29	(1.3)	9	(0.4)	0.0012
Modified CCI, ² mean (SD)	1.3	(1.6)	0.4	(1.1)	< 0.0001
Components of modified CCI, n (%)					
Rheumatic disease (excluding SSc) ³	741	(33.8)	47	(2.1)	< 0.0001
Chronic pulmonary disease ⁴	625	(28.5)	179	(8.2)	< 0.0001
Diabetes without chronic complication	187	(8.5)	204	(9.3)	0.3656
Any malignancy including leukemia and lymphoma	176	(8.0)	126	(5.7)	0.0023
Peripheral vascular disease	209	(9.5)	61	(2.8)	< 0.0001
Congestive heart failure	197	(9.0)	53	(2.4)	< 0.0001
Cerebrovascular disease	172	(7.8)	80	(3.6)	< 0.0001
Renal disease	142	(6.5)	37	(1.7)	< 0.0001
Mild liver disease	119	(5.4)	35	(1.6)	< 0.0001
Diabetes with chronic complications	64	(2.9)	49	(2.2)	0.1508
Myocardial infarction	42	(1.9)	11	(0.5)	< 0.0001

¹ The followup period was defined as the 12-month period following the index date. ² Excluded SSc diagnoses from the rheumatic disease component. ³ Includes giant systemic lupus erythematosus, sicca syndrome, dermatomyositis, polymyositis, rheumatoid arthritis, Felty syndrome, rheumatoid lung, and polymyalgia rheumatica. ⁴ Includes chronic airway obstruction, asbestosis, asthma, bronchiectasis, bronchitis, emphysema, extrinsic allergic alveolitis, pneumoconiosis, pulmonary heart diseases, pulmonary manifestations including secondary pulmonary hypertension, and respiratory conditions. SSc: systemic sclerosis; HRU: healthcare resource utilization; CCI: Charlson comorbidity index; CT: computed tomography; HRCT: high-resolution CT.

which \$16,269 were medical costs and \$5746 pharmacy costs) than matched controls (\$5977, of which \$4076 were medical costs and \$1901 pharmacy costs; all $p < 0.0001$). After adjustment, the adjusted difference between patients with SSc and matched controls was \$12,820 (SSc: \$18,069; matched

controls: \$5250) for total annual direct healthcare costs; \$9756 (SSc: \$13,024; matched controls: \$3268) for total annual medical costs, and \$2942 (SSc: \$4625; matched controls: \$1684) for annual pharmacy costs (all $p < 0.0001$; Table 4).

Work loss in the followup period. Unadjusted and adjusted

Table 3. Unadjusted and adjusted all-cause HRU in the followup period¹.

Variables	Unadjusted Analysis			Adjusted Analysis	
	Patients with SSc, n = 2192	Matched Controls, n = 2192	p	Patients with SSc vs Matched Controls	p
Proportion of patients with visits or admissions, n (%)				OR (95% CI)	
Any IP admission	688 (31.4)	238 (10.9)	< 0.0001	3.8 (3.2–4.5)	< 0.0001
Any ER visit	698 (31.8)	425 (19.4)	< 0.0001	1.9 (1.7–2.2)	< 0.0001
Any OP visit ²	2181 (99.5)	1851 (84.4)	< 0.0001	–	–
Any other visits ³	915 (41.7)	531 (24.2)	< 0.0001	2.2 (2.0–2.6)	< 0.0001
Annual no. visits or admissions, mean (SD)				IRR (95% CI)	
IP admissions	0.7 (2.1)	0.3 (2.3)	< 0.0001	2.4 (2.2–2.6)	< 0.0001
Total IP hospitalization days	3.7 (12.7)	1.1 (6.7)	< 0.0001	3.1 (2.9–3.4)	< 0.0001
ER visits	0.7 (2.5)	0.3 (1.2)	< 0.0001	2.0 (1.9–2.2)	< 0.0001
OP visits	23.8 (19.4)	10.3 (12.4)	< 0.0001	2.3 (2.2–2.4)	< 0.0001
Other visits ³	3.0 (7.6)	1.0 (3.4)	< 0.0001	2.9 (2.7–3.1)	< 0.0001

¹ The followup period was defined as the 12-month period following the index date. ² Model could not converge because 99.5% of patients with SSc had any OP visit. ³ Including laboratory tests and medical services at home. HRU: healthcare resource utilization; SSc: systemic sclerosis; IP: inpatient; ER: emergency room; OP: outpatient; IRR: incidence rate ratio.

Table 4. Unadjusted and adjusted direct healthcare and indirect costs (2016 US\$) in the followup period¹.

Variables	Unadjusted Analysis		Adjusted Analysis			
	Patients with SSc	Matched Controls	Patients with SSc	Matched Controls	Cost Difference	p
All-cause annual healthcare costs						
Total direct healthcare costs	22,016	5977	18,069	5250	12,820	< 0.0001
Total medical costs	16,269	4076	13,024	3268	9756	< 0.0001
IP	6502	1316	5967	1267	4701	< 0.0001
ER	708	248	638	240	398	< 0.0001
OP	8025	2365	6766	1942	4825	< 0.0001
Other	1035	148	837	182	656	< 0.0001
Pharmacy	5746	1901	4625	1684	2942	< 0.0001
Annual indirect costs						
Total indirect costs	5170	1663	4554	1451	3103	< 0.0001
Disability	1554	137	1513	151	1361	< 0.0001
Medically related absenteeism	3616	1526	3362	1333	2029	< 0.0001

¹ The followup period was defined as the 12-month period following the index date. Values are expressed as means. SSc: systemic sclerosis; IP: inpatient; ER: emergency room; OP: outpatient.

work loss was also significantly higher among patients with SSc than matched controls (Table 5). In particular, patients with SSc had more days of work loss (21.3 vs 6.8; adjusted IRR 2.6, 95% CI 2.1–3.2), composed of days of medically related absenteeism (11.0 vs 4.8; adjusted IRR 2.3, 95% CI 2.0–2.6) and days of disability (10.2 vs 2.0; adjusted IRR 2.1, 95% CI 1.7–2.7; all $p < 0.0001$). Additionally, the odds of any medically related absenteeism were significantly higher (aOR 6.3, 95% CI 2.4–16.6; $p = 0.0002$) and odds of any day of disability were numerically higher (aOR 2.2, 95% CI 0.9–5.1; $p = 0.0760$) for patients with SSc versus matched controls (Table 5).

Indirect costs in the followup period. Indirect costs (i.e., costs associated with work productivity loss due to disability or medically related absenteeism) were significantly higher for patients with SSc than for matched controls in both the unadjusted and adjusted analyses. Unadjusted indirect costs

were \$5170 (disability: \$1554; medically related absenteeism: \$3616) for patients with SSc versus \$1663 (disability: \$137; medically related absenteeism: \$1526) for matched controls (all $p < 0.0001$). The adjusted difference was \$3103 (SSc: \$4554; matched controls: \$1451) for total annual indirect costs, with \$1361 (SSc: \$1513; matched controls: \$151) for disability costs and \$2029 (SSc: \$3362; matched controls: \$1333) for medically related absenteeism costs (all $p < 0.0001$; Table 4).

DISCUSSION

Our present study sought to provide an updated estimate of the direct economic burden of SSc in the United States as well as to provide an estimate of the indirect economic burden of SSc, which has not been characterized in the literature. Using claims data, we found that patients with SSc had substantially greater HRU, work loss, and annual direct

Table 5. Unadjusted and adjusted work loss in the followup period¹.

Variables	Unadjusted Analysis			Adjusted Analysis	
	Patients with SSc, n = 233	Matched Controls, n = 233	p	Patients with SSc vs Matched Controls	p
Proportion of patients with any work loss, n (%)				OR (95% CI)	
Any day of work loss ²	233 (100.0)	207 (88.8)	—	—	—
Any day of disability	21 (9.0)	9 (3.9)	0.0285	2.2 (0.9–5.1)	0.0760
Any day of medically related absenteeism	227 (97.4)	206 (88.4)	0.0002	6.3 (2.4–16.6)	0.0002
Days of work loss, mean (SD)				IRR (95% CI)	
Total days of work loss	21.3 (45.8)	6.8 (19.4)	< 0.0001	2.6 (2.1–3.2)	< 0.0001
Days of disability	10.2 (46.6)	2.0 (18.3)	0.0076	2.1 (1.7–2.7)	< 0.0001
Days of medically related absenteeism	11.0 (9.3)	4.8 (6.3)	< 0.0001	2.3 (2.0–2.6)	< 0.0001

¹ The followup period was defined as the 12-month period following the index date. ² P value could not be calculated and model could not converge because all patients with SSc had any day of work loss. SSc: systemic sclerosis; IRR: incidence rate ratio.

healthcare and indirect costs than their matched controls without SSc. More specifically, compared to their matched controls, patients with SSc had IP admissions about 3 times more frequently and incurred all-cause annual direct healthcare costs that were nearly 3 times higher during the first year after diagnosis. The adjusted difference in total annual direct healthcare costs between patients with SSc and matched controls was \$12,820, mostly driven by medical costs (difference of \$9756). In addition, patients with SSc had about 14 more days of work loss due to disability or medically related absenteeism in the first year after diagnosis. In line with these results, total annual indirect costs were significantly higher for patients with SSc than their matched controls, with an adjusted cost difference of \$3103.

The finding that direct healthcare costs are significantly higher for patients with SSc than controls is consistent with the literature. A claims data study by Furst, *et al*¹⁸ reported unadjusted annual healthcare (medical and pharmacy) costs of \$21,625 for patients with SSc and \$6859 for matched controls, resulting in a cost difference of \$14,766. These costs are comparable to the unadjusted annual healthcare cost (\$22,016) for patients with SSc and cost difference (\$16,039) found in our current study. Furst, *et al* also reported adjusted annual healthcare costs of \$22,909 for patients with SSc and \$6620 for matched controls, resulting in a cost difference of \$16,288. The lower adjusted cost difference found in the current study (\$12,820) may be explained by the different definition of matched controls used in Furst, *et al*¹⁸. The difference may also reflect that the Furst, *et al* study was conducted among patients in a managed care organization, where patients included in the current study were enrolled in fee-for-service health plans. Nevertheless, our study and that by Furst, *et al* found largely comparable annual direct healthcare costs for patients with SSc and high incremental burden between patients with SSc and matched controls. This

suggests that the economic burden of SSc has remained high over the past decade despite the application of different treatment options or approaches.

This finding is also supported by a recent study by Fischer, *et al*¹⁹, which estimated first-year healthcare (medical and pharmacy) costs for patients with SSc at \$22,245 (2016 US\$) considering claims data from 2003 to 2014 but not including matched controls. The amount is similar to the first-year costs found in this study of \$22,016. Besides first-year costs, the current study also estimated all-cause annual direct healthcare costs during the second and third years after a diagnosis of SSc among patients with continuous health plan enrollment as an exploratory analysis (data not reported here). In the second and third years, average annual total costs for patients with SSc were estimated at \$19,119 and \$18,742, respectively (\$5921 and \$6108, respectively, for matched controls), which are comparable to \$20,050 in the second year and \$19,707 in the third year (all costs inflated to 2016 US\$), as reported in the Fischer, *et al* study¹⁹. Taken together, these results point to a substantial direct economic burden among patients with SSc. Moreover, it should be noted that neither Furst, *et al*¹⁸ nor Fischer, *et al*¹⁹ reported the indirect costs associated with SSc, which, as found in our current study, are significantly high. Thus, when both annual direct healthcare and indirect costs are taken into consideration, the overall burden of illness related to SSc becomes even more pronounced, further underscoring the existence of a high unmet need for more effective management of SSc.

Some limitations should be considered when interpreting the results of our study. First, our study may have underestimated the burden of illness of SSc given that it was assessed using claims submitted during the first year after diagnosis. Because its clinical heterogeneity makes SSc difficult to diagnose in a timely manner, disease onset may have occurred before a diagnosis of SSc was made and thus patients may

have incurred SSc-related costs and HRU before an SSc-related claim was submitted. Therefore, the true burden of SSc may be higher than the burden during the first year after a diagnosis of SSc. In addition, the later stages of the disease tend to have more chronic organ involvement, which may be associated with higher direct and indirect costs. Further, the study may have included patients who were initially diagnosed with SSc prior to the data period; because disease burden is also relatively high at diagnosis, the burden may have been underestimated by not identifying these patients' true diagnosis date. Further studies are needed to quantify such burden from disease onset over a longer period (> 3 yrs), given the progressive features of the disease. Additionally, patients who died or lost their job and/or insurance coverage because of SSc within 12 months post-index may have contributed higher costs but were not included, possibly leading to an underestimate of the overall cost burden of SSc. Second, some patients over 65 years of age could be partially covered by Medicare. The data record the portion of costs covered by the private insurers but not the portion of costs covered by Medicare and thus their claims data may have been incomplete, leading to underestimation of the burden within this group of patients. Third, our study assumed that each hospitalization day and emergency department visit accounted for a full day of work loss, while each outpatient or other visit accounted for half a day of work loss, which may not reflect true work loss incurred by patients. Other limitations inherent to claims data should also be taken into consideration. Disease cohorts were defined based on diagnosis codes; because claims data are subject to error or omissions, patients may have been misclassified and incorrectly included in or excluded from one of the 2 cohorts. Further, because claims data do not provide information on disease severity, our study could not assess the effect of SSc severity on the burden of illness. Also, because the data used in our study were limited to patients with employer-sponsored health plans, the results may not be generalizable to other patient populations. Finally, as with any retrospective observational study, associations but no causal relationships should be inferred.

This claims data study found that patients with SSc had a substantially higher burden of illness than their matched controls, as evidenced by greater HRU, work loss, and annual direct healthcare and indirect costs. This represents an updated estimate of the direct economic burden and the first estimate of the indirect economic burden associated with SSc in the United States. The substantial burden of illness of SSc found in this study underscores the need for more effective disease management that can potentially improve clinical outcomes and thus reduce HRU, costs, and work loss among patients with SSc.

ACKNOWLEDGMENT

Medical writing assistance was provided by Cinzia Metallo, PhD, an employee of Analysis Group Inc.

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